

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 09/118,730
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Inventors: Ellington M. Beavers et al
Title: METHOD OF MAKING FREE ACIDS
FROM POLYSACCHARIDE SALTS
Examiner: E. White
Art Unit: 1623
File No.: 281-28



THIRD DECLARATION OF ELLINGTON M. BEAVERS UNDER RULE 132

Ellington M. Beavers hereby declares as follows:

1. I am one of the named joint inventors in the above-identified application. I have read the Official Action of October 14, 1999, and I make this Declaration in response thereto.

2. This Declaration covers two subjects. First, the Examiner has held that, to be patentable, the product made by the claimed process must have unexpected or surprising properties. In response, this Declaration will explain the unexpected and surprising benefit of the pure hyaluronic acid made by my invention. Secondly, this Declaration records another graphic illustration of the confusion of nomenclature, in the industry, between "hyaluronic acid" and "sodium hyaluronate".

Surprising Benefit of Free Hyaluronic Acid

3. As described more fully in my U.S. Patent Nos. 4,801,475, 5,023,114, and 5,037,677, cited in the present application, a mucopolysaccharide is used to produce a hydrophilic, lubricious coating (a "top coat") for an object that is intended to be placed permanently or temporarily in the body. The cited patents teach coating the object first with a "tie-coat", i.e. a material which adheres tightly to the underly-

ing substrate, and which also has functional groups which provide a chemical graft with the mucopolysaccharide. A preferred mucopolysaccharide is hyaluronic acid, which, until the making of my present invention, had only been available as a sodium salt. The polysaccharide has both hydroxyl and carboxyl groups. The polysaccharide must be chemically attached to the tie-coat in order to produce a biocompatible, lubricious surface that is not washed away by aqueous body fluids.

4. When one incorporates a poly-isocyanate into the organic-soluble tie-coat, isocyanate groups become available at the interface with the polysaccharide layer, and react with hydroxyl groups in the polysaccharide to provide the chemical attachment required.

5. But the polyisocyanate is not water-soluble and cannot be incorporated into an aqueous emulsion polymer that often is preferred as the tie-coat. A poly-aziridine is water-soluble and can be incorporated into the emulsion or into the aqueous solution of the polysaccharide. The poly-aziridine does not react with sodium hyaluronate, but does react with hyaluronic acid to provide the chemical attachment required.

6. Thus, the polyisocyanate cannot be used with aqueous coatings. Polyaziridine can be used with aqueous coatings, but only if the free hyaluronic acid is used as the top coat. The sodium salt of the polysaccharide will not work with polyaziridines.

7. Furthermore, hyaluronic acid can be joined with other molecules of hyaluronic acid in the presence of the polyaziridine, and this coating build-up is often highly desirable for a variety of reasons. Sodium hyaluronate cannot be used in the same way, because the salt would require the polyisocyanate, but the polyisocyanate is insoluble in water and cannot be used in an aqueous medium.

8. The facts outlined in Paragraphs 4-7, above, were not generally known at the time my invention was made, and, to the best of my knowledge, are still not generally appreciated. Thus, in the past, there was no particular reason to believe that the free-acid form of hyaluronic acid would have particular utility. Indeed, as explained earlier, the academic and business worlds have long used the term "hyaluronic acid" to refer both to the free acid and its sodium salt. For practical purposes, the distinction between the two substances was considered to be of little or no significance. But as a result of my discoveries, it became apparent that the free-acid form of hyaluronic acid had special properties which made it especially useful in forming hydrophilic, lubricious coatings.

9. Thus, I recognized the special advantage and benefits of the free-acid form of hyaluronic acid, namely that it can be used with polyaziridines to product a hydrophilic, lubricious coating, wherein the first coat (the tie-coat) is an aqueous emulsion polymer. The results obtained from the free hyaluronic acid, which is the product of my invention, are both surprising and beneficial, and were not known in the industry or in the academic world.

Confusion between Hyaluronic Acid and its Sodium Salt

10. In my prior Declaration, I explained that there has been considerable confusion, both in industry and in the academic world, concerning hyaluronic acid. The term "hyaluronic acid" is used, when what is really meant is the sodium salt. The following paragraphs summarize another recent incident that demonstrates this point.

11. On or about January 10, 2000, I called TRI-K Industries, Inc.,

a chemical supplier, to order a quantity of sodium hyaluronate. When I placed the order by telephone, the order taker questioned whether the company handled such material. I assured her that we had purchased it several times from her company. After consulting the company catalog, the order taker asked whether I meant "hyaluronic acid powder". Rather than debate the nomenclature problem with her, I ordered the "hyaluronic acid powder". Attached as Exhibit A is a copy of the Order Acknowledgment, showing the order for "hyaluronic acid powder".

12. The shipment arrived, and was accompanied by a Certificate of Analysis, a copy of which is attached as Exhibit B. The last line of the certificate shows that the product is sodium hyaluronate. It is not the free acid form. This is one more example showing that the term "hyaluronic acid" is used incorrectly to refer to the sodium salt.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Feb. 15, 2000


Ellington M. Beavers